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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,256	10/02/2001	Naoyuki Fukuchi	214595US0PCT	8955

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EXAMINER	
DESAI, ANAND U	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,256	FUKUCHI ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *11-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *July 17, 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to Amendment filed on July 17, 2006. Claims 11-15 have been withdrawn previously. Claims 1-10 are currently pending and are under examination.

Specification

2. The disclosure is objected to because of the following informalities:

3. The last sentence in the first indented paragraph in the Background Art section is unclear; The phrase, "...proteins that are not necessarily be required to be a dimer are also known" is grammatically incorrect.

4. The drawing (Figure 6) sets forth peptide sequences (peptide numbers: 2-6 in Figure 6b) without reciting the corresponding sequence identifiers (SEQ ID NO:__). Applicant is required to comply with requirements for patent application containing amino acid sequence disclosure. Suggest placing SEQ ID NO: next to each peptide sequence in Figure 6b.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of purifying the α-chain of the snake venom protein CHH-B that is bonded with polyethylene glycol between the thiol group of the α-subunit and the

polyethylene glycol, does not reasonably provide enablement for the method of purifying any subunit peptide originating from any oligomeric protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

1.) The nature of the invention: the invention is drawn to a method for purifying a subunit peptide originating from an oligomeric protein having disulfide bonds within a subunit and between subunits, which comprises refolding the subunit peptide by denaturing the oligomeric protein or its subunit peptide in a solution with a protein-denaturing agent and removing the denaturing agent from the solution in the presence of polyoxyalkyl polyether having a functional group that reacts with a thiol group to allow the subunit peptide to bind to the polyoxyalkyl polyether via the reaction between the thiol group of the subunit peptide and the functional group of the polyoxyalkyl polyether that reacts with a thiol group, and isolating the subunit peptide bonded to the polyoxyalkyl polyether from the solution. The method further comprises that the subunit peptide bonded to the polyoxyalkyl polyether has the physiological activity of the oligomeric protein, and in another embodiment has an activity of inhibiting a physiological activity of the oligomeric protein.

2.) The breadth of the claims: the claims are broad in that any subunit of any oligomeric protein having a disulfide bond within a subunit and between subunits is expected to either have the physiological activity of the oligomeric protein, or the activity of inhibiting a physiological activity of the oligomeric protein.

3.) The predictability or unpredictability of the art: / 7.) The state of the prior art: there is predictability in the art with regard to the different functional effects of peptide subunits compared to the functional effect of an oligomeric protein composed of the respective peptide subunits. Rowlett et al. describe the different substrate and reaction specificity of wild-type β_2 compared to wild-type $\alpha_2\beta_2$ of tryptophan synthetase. The wild-type $\alpha_2\beta_2$ complex has much greater activity with L-serine than with β-chloro-L-alanine, whereas the opposite is true with the β_2 subunit (see page 2965, Right column, Mutations Alter Substrate and Reaction Specificity section, 1st and 3rd sentences, and Figure 4A and B WT columns). Perutz et al. describe the cooperative effect of oxygen binding by the tetramer of hemoglobin. Hemoglobin is an oligomeric protein whose tetramer structure confers cooperative binding of oxygen (see entire document, particularly page 7, Structure and Function of Hemoglobin section).

There is unpredictability in the art with regard to the functional effects of coupled polyoxyalkyl polyether polymers to peptides. Basu et al. state that "conjugates composed of PEG and receptor-binding ligands frequently exhibit diminution or even loss of bioactivity, and these compounds may also demonstrate substantial product heterogeneity." (see page 619, left column, 1st indented paragraph, 5th sentence).

4.) & 5.) The amount of direction or guidance presented:/The presence or absence of working examples: the example describes the structure of the α-chain of the snake venom protein CHH-B and functional effect of conjugating polyethylene glycol to the cysteine residue located at amino acid residue 81 thereby reducing platelet aggregation due to vWF interaction. The specification provides guidance with respect to the CHH-B protein discussed in the working examples but provides no guidance whatsoever in selecting which other protein subunits might

have the needed conformations to have the physiological activity of the oligomeric protein, or the activity of inhibiting a physiological activity of the oligomeric protein. Further, no guidance is provided as to how to determine which oligomeric protein subunits might work.

6.) The quantity of experimentation necessary: there is a large quantity of experimentation necessary to determine which subunits are capable of forming the physiological activity of the oligomeric protein, or has an activity of inhibiting a physiological activity of the oligomeric protein.

8.) Level of skill in the art: the level of skill in this art is high.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

7. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that

"the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention*. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

In the instant case, the claims are drawn to a method for purifying any subunit peptide originating from an oligomeric protein having disulfide bonds within a subunit and between subunits, which comprises refolding the subunit peptide by denaturing the oligomeric protein or its subunit peptide in a solution with a protein-denaturing agent and removing the denaturing agent from the solution in the presence of polyoxyalkyl polyether having a functional group that reacts with a thiol group to allow the subunit peptide to bind to the polyoxyalkyl polyether via the reaction between the thiol group of the subunit peptide and the functional group of the polyoxyalkyl polyether that reacts with a thiol group, and isolating the subunit peptide bonded to the polyoxyalkyl polyether from the solution. The method further comprises that the subunit peptide bonded to the polyoxyalkyl polyether has the physiological activity of the oligomeric protein, and in another embodiment has an activity of inhibiting a physiological activity of the oligomeric protein.

The example describes the structure of the α-chain of the snake venom protein CHH-B and functional effect of conjugating polyethylene glycol to the cysteine residue located at amino acid residue 81 to reduce platelet aggregation due to vWF binding. The specification provides

guidance with respect to the CHH-B protein discussed in the working examples but provides no guidance whatsoever in selecting which other protein subunits might have the needed conformations to have the physiological activity of the oligomeric protein, or the activity of inhibiting a physiological activity of the oligomeric protein. Further, no guidance is provided as to how to determine which oligomeric protein subunits might work.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad genus. Claim to all peptides with disulfide bonds within a subunit and between subunits is broadly generic. The possible variations are enormous. Since the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of all subunit peptides beyond those disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus.

While having written description of the α-chain of the snake venom protein CHH-B and functional effect of conjugating polyethylene glycol to the cysteine residue located at amino acid residue 81 identified in the specification tables and/or examples, the specification is devoid of any other subunit peptide that qualify for the functional characteristics claimed.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*,

736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 9:00 a.m. - 5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

September 25, 2006

ROBERT A. WAX
PRIMARY EXAMINER